EXHIBIT C

IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF WEST VIRGINIA
CHARLESTON DIVISION

IN RE: ETHICON, INC., PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION	**Master File No. 2:12-MD-02327** **MDL 2327**
	JOSEPH R. GOODWIN **U.S. DISTRICT JUDGE**

GENERAL SACROCOLPOPEXY REPORT OF

PETER JEPPSON, MD, FACOG, FACS

I. Background and Qualifications

I graduated from Saint Louis University School of Medicine in Saint Louis, Missouri in 2006, and then completed my residency in Obstetrics and Gynecology at the Cleveland Clinic and Case Western Reserve University MetroHealth Medical Center in Cleveland, Ohio in 2010. Following this I completed additional fellowship training to acquire advanced expertise in Female Pelvic Medicine and Reconstructive Pelvic Surgery, colloquially called Urogynecology, at the Warren Alpert Medical School of Brown University, which I completed in 2013. I passed written and oral examinations for General Obstetrics & Gynecology and Female Pelvic Medicine & Reconstructive Surgery on my first attempt. I am subsequently board-certified by the American Board of Obstetrics and Gynecology, in both Obstetrics and Gynecology and sub-specialty certified in Female Pelvic Medicine and Reconstructive Surgery. In addition, I am a fellow of the American College of Obstetrics and Gynecology and a fellow of the American College of Surgeons. I am currently an Assistant Professor and Director of the Division of Urogynecology at University of New Mexico. I have published over 40 peer-reviewed manuscripts including systematic reviews on urinary incontinence and pelvic organ prolapse. My qualifications, experience, and publications are further detailed in my curriculum vitae, which is provided with this report.

All of my opinions, and the basis of those opinions, are true and correct to the best of my knowledge and belief, including those related to scientific and medical issues, which I believe are true and correct to a reasonable degree of scientific and medical certainty. I do, however, reserve the right to supplement this report and my opinions in light of any additional material or information provided to me, including any reports submitted and/or any other discovery that is taken in this case. The opinions in this report are based on my education, training, experience, review of published medical literature, and the other materials that have been provided to me, which are included on my list of materials.

I trained at premier FPMRS institutions for both residency and fellowship. This allowed me to learn and become proficient in all non-surgical and surgical treatment modalities for prolapse. From a surgical perspective, I am well-versed/proficient/competent in all possible treatment options. Since completing fellowship in 2013, I have been extensively involved in teaching residents and fellows at the University of New Mexico. In addition, I have conducted and published multiple systematic reviews, including reviews regarding prolapse treatments. Additional details regarding that experience is set forth in my CV. In addition to these endeavors, I have taught numerous fellows at the University of New Mexico how to perform these surgeries.

I am being compensated at the rate of $450 per hour for my preparation of this report. I have testified as an expert witness in one deposition in the last four years, in the Silva v. Ethicon matter on 10/8/2018.

II. Pelvic Organ Prolapse

Pelvic organ prolapse (POP) is defined as the descent of one or more pelvic organs.[1] Different types of prolapse can occur depending on which vaginal compartment has "fallen"; options include 1) apical or upper vaginal prolapse, this includes uterine prolapse or vaginal vault prolapse if it occurs following a hysterectomy, 2) anterior wall vaginal prolapse, which is when the bladder has dropped, or 3) posterior vaginal wall prolapse, which is when the rectum or perineum drops.[2] The etiology of POP is complicated. There are many risk factors for POP, including pregnancy, vaginal childbirth, connective tissue abnormalities, genetics, denervation or weakness of the pelvic floor, increased age, increased BMI, prior hysterectomy, menopause, smoking, weight loss, chronic cough, chronic constipation, or other factors associated with chronically increased intra-abdominal pressure.[3] POP is very common and estimated to affect 40-60% of parous women with approximately 15% of women electing to proceed with surgical correction.[4]

POP often results in a variety of patient-reported symptoms including a sensation of pelvic heaviness and the feeling of a lump or bulge protruding from the vagina.[5] Others report inability to place or use a tampon, vaginal dryness or irritation from the prolapse rubbing on clothing.[6] Many women report the need to manually reduce the prolapse by using their fingers to push the POP back inside in order to urinate or defecate. POP should be evaluated in the context of patient bother. Vaginal anatomy changes with age and after childbirth, so prolapse should not only be an anatomic evaluation. Many women will become symptomatic when the leading edge of the prolapse approaches or protrudes beyond the hymen. Several staging systems exist to report and compare how far the vagina and pelvic organs have prolapsed. The most common grading system is the Pelvic Organ Prolapse – Quantification or POP-Q.[7] This system was described back in 1996 and is typically used in research studies and clinic prolapse to determine if patients have no, mild, moderate, or severe prolapse reported as stage 0 to stage 4 prolapse.

There are numerous non-surgical and surgical treatments. Non-surgical options include no treatment or watchful waiting, pelvic floor muscle exercises (Kegels), pelvic floor physical

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[1] Maher C, et al., Surgical management of pelvic organ prolapse in women. Cochrane Database Syst Rev. 2013 Apr 30;(4):CD004014.
[2] Maher C, et al., Surgical management of pelvic organ prolapse in women. Cochrane Database Syst Rev. 2013 Apr 30;(4):CD004014.
[3] Maher C, et al., Surgery for women with anterior compartment prolapse. Cochrane Database Syst Rev. 2016 Nov 30;11:CD004014; Hagen S and Stark D, Conservative prevention and management of pelvic organ prolapse in women. Cochrane Database Syst Rev. 2011 Dec 7;(12):CD003882; Barber MD, Pelvic organ prolapse. BMJ. 2016 Jul 20;354:i3853.
[4] Haya N, et al., Perioperative interventions in pelvic organ prolapse surgery. Cochrane Database Syst Rev. 2018 Aug 19;8:CD013105; AUGS Pelvic Organ Prolapse fact sheet, available at https://www.voicesforpfd.org/assets/2/6/POP.pdf.
[5] Maher C, et al., Surgery for women with anterior compartment prolapse. Cochrane Database Syst Rev. 2016 Nov 30;11:CD004014.
[6] AUGS Pelvic Organ Prolapse fact sheet, available at https://www.voicesforpfd.org/assets/2/6/POP.pdf.
[7] Bump RC, et al., The standardization of terminology of female pelvic organ prolapse and pelvic floor dysfunction. Am J Obstet Gynecol. 1996 Jul;175(1):10-7.

therapy, or pessary.[8] Surgical procedures can be broadly categorized as obliterative procedures such as colpocleisis or reconstructive surgeries. Reconstructive surgeries can be further subdivided into native tissue repair or mesh-augmented repairs.[9]

III. Non-Surgical Treatment Options for POP

Conservative, or non-surgical POP treatments include no treatment, pelvic floor muscle exercises, pelvic floor physical therapy (PFPT), or pessary. A recent Cochrane review found that 6 months of PFPT provides both anatomic and symptomatic improvement of prolapse.[10] Pessaries are also a very common treatment option. A pessary is typically a silicone ring that can be inserted into the vagina to physically support the vaginal walls and hold the prolapsed organs inside the vagina.[11] Although pessaries are commonly used, there are few publications on the indications, management and effectiveness or pessary treatment for POP.[12] They can cause vaginal odor, vaginal discharge, bleeding, erosion, ulceration, infection, and other complications.[13] Nevertheless, risks are minimal and up to 77% of clinicians use pessaries in the initial management of POP.[14]

IV. Surgical Treatment Options for POP

Many different surgical procedures have been described for POP. These can be separated into obliterative, native tissue, or graft- or mesh-augmented repairs. Obliterative procedures, such as colpocleisis or colpectomy reduce the POP by surgically closing the vagina. This surgery precludes any future penetrative intercourse. Native tissue repairs utilize the patient's own tissue with suture to reduce prolapse and restore proper anatomy. Native tissue repairs include uterosacral ligament suspension, sacrospinous ligament suspension, anterior colporrhaphy, posterior colporrhaphy, and perineorrhaphy. Finally, mesh- or graft-augmented repairs can be performed, placing additional material in an attempt to fortify the surgical repair in order to improve the durability and decrease the risk of recurrent prolapse.

A Cochrane review that included 5,954 women found that apical vaginal prolapse was best treated with abdominal sacral colpopexy based on lower recurrent apical prolapse and decreased dyspareunia.[15] Inadequate support of the vaginal apex can lead to failures in the

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[8] AUGS Pelvic Organ Prolapse fact sheet, available at https://www.voicesforpfd.org/assets/2/6/POP.pdf.
[9] Haya N, et al., Perioperative interventions in pelvic organ prolapse surgery. Cochrane Database Syst Rev. 2018 Aug 19;8:CD013105.
[10] Hagen S and Stark D, Conservative prevention and management of pelvic organ prolapse in women. Cochrane Database Syst Rev. 2011 Dec 7;(12):CD003882.
[11] Bugge C, et al., Pessaries (mechanical devices) for pelvic organ prolapse in women. Cochrane Database Syst Rev. 2013 Feb 28;(2):CD004010.
[12] Barber MD, Pelvic organ prolapse. BMJ. 2016 Jul 20;354:i3853.
[13] Russell JK, The dangerous vaginal pessary. BMJ. 1961;16;2(5267):1595-1597.
[14] Bugge C, et al., Pessaries (mechanical devices) for pelvic organ prolapse in women. Cochrane Database Syst Rev. 2013 Feb 28;(2):CD004010.
[15] Maher C, et al., Surgical management of pelvic organ prolapse in women. Cochrane Database Syst Rev. 2013 Apr 30;(4):CD004014.

posterior and anterior compartments.[16] When native tissue repairs were compared to vaginal mesh kits, there was no difference in patient-perceived symptom resolution, however the recurrence rate based on anatomic evaluation was higher in the native tissue group than the mesh kit group. The polypropylene mesh erosion rate was 18% in these studies and almost 10% of women required repeat surgery for mesh erosion.[17] This led the authors to conclude: "sacral colpopexy has superior outcomes to a variety of vaginal procedures including sacrospinous colpopexy, uterosacral colpopexy and transvaginal mesh. These benefits must be balanced against a longer operating time, longer time to return to activities of daily living, and increased cost of the abdominal approach."[18]

A Cochrane review specific to anterior vaginal prolapse included 3,332 women and various types of surgical interventions reported the following conclusions.[19] 1) Use of biological grafts, did not seem to provide any benefit to native tissue repairs. 2) When native tissue was compared to polypropylene mesh patients were more likely to notice symptoms of prolapse after a native tissue repair, were more likely to undergo repeat surgery for recurrent prolapse, however, more patients with polypropylene mesh required repeat surgery because of mesh exposure. Dyspareunia rates were not different between groups. 3) There does not appear to be any benefit for absorbable mesh over native tissue repairs with respect to patient reported prolapse, or repeat surgery for recurrent prolapse. They concluded that there is little evidence to support the use of absorbable mesh or biological grafts in anterior compartment prolapse. They also concluded that there are distinct advantages and disadvantages associated with the use of transvaginal polypropylene mesh, and that because significant adverse events were reported with anterior transvaginal polypropylene mesh, this should not be used as a first-line intervention for anterior compartment prolapse. They also point out that most of the transvaginal mesh kits are no longer available.

The increased rates of complications identified with transvaginal mesh for the treatment of POP led the US Food and Drug Administration to issue public health notifications.[20] As already described, erosion of transvaginal mesh can occur, which can result in vaginal bleeding, pelvic pain, dyspareunia, or other pelvic dysfunction. It is important to note that transabdominal mesh placement as is done with sacrocolpopexy has not come under similar scrutiny because of lower risk of mesh complications and more favorable risk-benefit profile.[21]

All pelvic floor surgeries—including all surgical treatments for pelvic organ prolapse—carry a potential risk of pelvic pain, vaginal pain, or dyspareunia. In a systematic review and meta-analysis I co-authored as part of the Society of Gynecologic Surgeons Systematic Review Group,

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[16] Hsu Y, et al., Anterior vaginal wall length and degree of anterior compartment prolapse seen on dynamic MRI. Int Urogynecol J Pelvic Floor Dysfunct. 2008 Jan 27;19(1):137–142.
[17] Maher C, et al., Surgical management of pelvic organ prolapse in women. Cochrane Database Syst Rev. 2013 Apr 30;(4):CD004014.
[18] Maher C, et al., Surgical management of pelvic organ prolapse in women. Cochrane Database Syst Rev. 2013 Apr 30;(4):CD004014.
[19] Maher C, et al., Surgery for women with anterior compartment prolapse. Cochrane Database Syst Rev. 2016 Nov 30;11:CD004014.
[20] Barber MD, Pelvic organ prolapse. BMJ. 2016 Jul 20;354:i3853.
[21] Barber MD, Pelvic organ prolapse. BMJ. 2016 Jul 20;354:i3853.

our analysis showed that the rate of dyspareunia with mesh sacrocolpopexy was significantly lower than it was with native tissue vaginal prolapse repairs.[22] It has also been demonstrated that untreated vaginal prolapse can negatively affect sexual function and body image[23] so simply ignoring vaginal prolapse is not typically a better option for patients.

De novo dyspareunia has been reported to occur in 4% of women after an anterior colporrhaphy.[24] Dyspareunia following posterior colporrhaphy has been reported at rates of up to 57%.[25] Results from a prior systematic review demonstrated no difference in postoperative sexual function between mesh sacrocolpopexy and native tissue vaginal repairs.[26] A separate Cochrane review reported that abdominal sacral colpopexy was had higher anatomic success rates and less dyspareunia than vaginal sacrospinous ligament fixation, which is a type of native tissue repair.[27] The rare postoperative complication of de novo dyspareunia is not the result of a product defect or any inherent characteristic of the type 1 polypropylene sacrocolpopexy mesh.

Abdominal, robotic, or laparoscopic sacrocolpopexy is an excellent option for advanced-stage prolapse or recurrent prolapse following attempted native tissue repair. Sacrocolpopexy with meshes like Prolene mesh and Gynemesh PS, which are macroporous, has been recognized as the standard of care for the treatment of apical prolapse for many years.[28] For many years, surgeons have also been performing sacrocolpopexies with Type I polypropylene mesh

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[22] Siddiqui NY, et al., Mesh Sacrocolpopexy Compared With Native Tissue Vaginal Repair: A Systematic Review and Meta-analysis. Obstet Gynecol. 2015 Jan;125(1):44-55.

[23] Zielinski R, Miller J, Low LK, et al. The relationship between pelvic organ prolapse, genital body image, and sexual health. Neurourol Urodyn 2012;31(7):1145–1148. Female Pelvic Med Reconstr Surg 2017;23: 281–287.

[24] Maher C, et al., Surgical management of pelvic organ prolapse in women. Cochrane Database Syst Rev 2013;(4):CD004014; Schimpf MO, et al., Sling surgery for stress urinary incontinence in women: a systematic review and metaanalysis. Am J Obstet Gynecol 2014;211:71.e1-27

[25] Karram M and Maher C, Surgery for posterior vaginal wall prolapse. Int Urogynecol J 2013;24:1835-1841 (noting a mean postoperative dyspareunia rate of 18% (range 5-45%) after traditional posterior colporrhaphy); Komesu YM, et al., Posterior repair and sexual function. Am J Obstet Gynecol 2007 Jul;197(1):101.e1-6 (noting a post-operative dyspareunia rate of 57%); Kahn MA and Stanton SL, Posterior colporrhaphy: its effects on bowel and sexual function. Br J Obstet Gynaecol. 1997 Jan;104:822-86.

[26] Siddiqui NY, et al., Mesh Sacrocolpopexy Compared With Native Tissue Vaginal Repair: A Systematic Review and Meta-analysis. Obstet Gynecol. 2015 Jan;125(1):44-55.

[27] Maher C, et al., Surgical management of pelvic organ prolapse in women. Cochrane Database Syst Rev. 2013 Apr 30;(4):CD004014.

[28] Schettini M, et al., Abdominal sacral colpopexy with prolene mesh. Int Urogynecol J Pelvic Floor Dysfunct. 1999;10(5):295-9; Maher CF, et al., Laparoscopic sacral colpopexy versus total vaginal mesh for vaginal vault prolapse: a randomized trial. Am J Obstet Gynecol. 2011 Apr;204(4):360.e1-7; Baker KR, et al., Colposacropexy with Prolene mesh. Surg Gynecol Obstet. 1990 Jul;171(1):51-4; Mahendran D, et al., Laparoscopic sacrocolpopexy in the management of vaginal vault prolapse. Gynaecological Endoscopy 1996;5:217-222; Diana M, et al., Treatment of vaginal vault prolapse with abdominal sacral colpopexy using prolene mesh. Am J Surg. 2000 Feb;179(2):126-8; Pilsgaard K and Mouritsen L. Follow-up after repair of vaginal vault prolapse with abdominal colposacropexy. Acta Obstet Gynecol Scand. 1999 Jan;78(1):66-70; Agarwala N, et al., Laparoscopic sacral colpopexy with Gynemesh as graft material--experience and results. J Minim Invasive Gynecol. 2007 Sep-Oct;14(5):577-83; Maher C, et al., Surgical management of pelvic organ prolapse in women: a short version Cochrane review. Neurourol Urodyn. 2008;27(1):3-12; Stepanian AA, et al., Risk of mesh extrusion and other mesh-related complications after laparoscopic sacral colpopexy with or without concurrent laparoscopic-assisted vaginal hysterectomy: experience of 402 patients. J Minim Invasive Gynecol. 2008 Mar-Apr;15(2):188-96.

laparoscopically,[29] which has been shown to have the lowest recurrence rates.[30] Several systematic reviews demonstrate improved anatomic durability with mesh sacrocolpopexy with no other differences noted between the two surgical approaches.[31] Gilleran and colleagues noted in 2010 that "[t]he current 'gold standard' surgical repair for apical prolapse is the abdominal mesh sacrocolpopexy."[32] Nygaard and colleagues have observed that "abdominal sacrocolpopexy is the most durable operation for advanced POP and serves as the criterion standard against which other operations are compared."[33] Barber and colleagues noted in 2013 that abdominal sacrocolpopexy "has a higher success rate than sacrospinous colpopexy with less SUI and postoperative dyspareunia for vault prolapse" and that abdominal sacrocolpopexy utilizing polypropylene mesh yields superior outcomes compared to procedures utilizing fascia lata, porcine dermis, and small intestine submucosa.[34] We also found this in a systematic review and meta-analysis that I co-authored, "data favor mesh sacrocolpopexy over native tissue vaginal apex repairs in providing anatomic success. This is particularly evident for the anterior and apical compartments."[6] A survey published in 2016 of AUGS and IUGA members showed that 99% of the respondents used polypropylene mesh for sacrocolpopexy procedures.[35] Sacrocolpopexies are increasingly performed laparoscopically and robotically rather than via an open technique, as the more minimally invasive techniques result in less pain and fewer complications.[36] Laparoscopic and robotic sacrocolpopexies have been shown to have comparable efficacy, but the former is performed more frequently due to reduced cost.[37]

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[29] Di Marco DS, et al., Robotic-assisted laparoscopic sacrocolpopexy for treatment of vaginal vault prolapse. Urology. 2004 Feb;63(2):373-6; Sarlos D, et al., Laparoscopic sacrocolpopexy for uterine and post-hysterectomy prolapse: anatomical results, quality of life and perioperative outcome—a prospective study with 101 cases. Int Urogynecol J Pelvic Floor Dysfunct. 2008 Oct;19(10):1415-22; Agarwala N, et al., Laparoscopic sacral colpopexy with Gynemesh as graft material—experience and results. J Minim Invasive Gynecol. 2007 Sep-Oct;14(5):577-83; Mahendran D, et al., Laparoscopic sacrocolpopexy in the management of vaginal vault prolapse. Gynaecological Endoscopy 1996;5:217-22.

[30] Dandolu V, et al., Mesh complications and failure rates after transvaginal mesh repair compared with abdominal or laparoscopic sacrocolpopexy and to native tissue repair in treating apical prolapse. Int Urogynecol J. 2017 Feb 25;28(2):215-22.

[31] Siddiqui NY, et al., Mesh Sacrocolpopexy Compared With Native Tissue Vaginal Repair: A Systematic Review and Meta-analysis. Obstet Gynecol. 2015 Jan;125(1):44-55; Maher C, et al., Surgical management of pelvic organ prolapse in women. Cochrane Database Syst Rev. 2013 Apr 30;(4):CD004014.

[32] Gilleran JP, Johnson M, Hundley A. Robotic-assisted laparoscopic mesh sacrocolpopexy. Ther Adv Urol. 2010 Oct;2(5-06):195-208; Diwadkar GB, et al., Complication and reoperation rates after apical vaginal prolapse surgical repair: a systematic review. Obstet Gynecol. 2009 Feb;113(2 Pt 1):367-373.

[33] Nygaard I, et al., Long-term Outcomes Following Abdominal Sacrocolpopexy for Pelvic Organ Prolapse. JAMA 2013 309(19):2016-24.

[34] Barber MD and Maher C, Apical prolapse. Int Urogynecol J. 2013;24:1815-33.

[35] O'Sullivan OE, et al., Sacrocolpopexy: is there a consistent surgical technique? Int Urogynecol J. 2016 May;27(5):747-50.

[36] Linder BJ, et al., A National Contemporary Analysis of Perioperative Outcomes of Open versus Minimally Invasive Sacrocolpopexy. J Urol. 2018 Oct;200(4):862-867; Coolen A-LWM, et al., The treatment of post-hysterectomy vaginal vault prolapse: a systematic review and meta-analysis. Int Urogynecol J. 2017 Dec 16;28(12):1767-83; De Gouveia De Sa M, et al., Laparoscopic versus open sacrocolpopexy for treatment of prolapse of the apical segment of the vagina: a systematic review and meta-analysis. Int Urogynecol J. 2016 Jan 7;27(1):3-17.

[37] Callewaert G, et al., Laparoscopic versus robotic-assisted sacrocolpopexy for pelvic organ prolapse: a systematic review. Gynecol Surg. 2016 May 26;13(2):115-123; Paraiso MFR, Jelovsek JE, Frick A, Chen CCG, Barber MD. Laparoscopic Compared With Robotic Sacrocolpopexy for Vaginal Prolapse. Obstet Gynecol. 2011 Nov;118(5):1005–13; De Gouveia De Sa M, et al., Robotic versus laparoscopic sacrocolpopexy for treatment of

Abdominal sacrocolpopexy utilizing permanent mesh like Prolene mesh and Gynemesh PS has decreased probability for recurrent vaginal prolapse. In the 2015 SGS systematic review, we reported that in RCTs comparing native tissue vaginal prolapse repairs compared with mesh sacrocolpopexy in women with apical prolapse, there was a significantly greater likelihood of anatomic "success" with mesh sacrocolpopexy compared to native tissue vaginal repairs. Non-randomized comparative studies corroborated those results. Three cohort studies demonstrated a significantly higher likelihood of anatomic success with mesh sacrocolpopexy, and three underpowered cohort studies showed no significant differences between the techniques. We concluded that "moderate quality data favors mesh sacrocolpopexy over native tissue vaginal apex repairs in providing anatomic success." We noted that this result was "particularly evident for the anterior and apical compartments."[38]

A multi-national group of surgeons conducted a systematic review of the published literature up to September 2015 to develop evidence-based recommendations regarding sacrocolpopexy. They reported that "monofilament polypropylene mesh is the graft of choice and the laparoscopic approach is the preferred technique . . . ." and that "sacrocolpopexy is the preferred procedure for vaginal apical prolapse."[39]

Graft materials other than synthetic polypropylene mesh have been used for sacrocolpopexy surgery but the "standard of care favors the utilization of nonabsorbable, type I polypropylene for fixation in sacrocolpopexy surgeries."[40]

The mesh used in the Prolene mesh and Gynemesh PS is made of Prolene polypropylene, which has been used in surgeries for decades. The mesh is is Type I macroporous, lightweight knitted monofilament mesh, which is known for its biocompatibility.[41] Polypropylene suture has been used extensively in gynecologic, urologic, cardiac, orthopedic, thoracic, and general surgery. Polypropylene mesh has also been used extensively for the past 30 years to surgically repair abdominal wall hernias.[42] Various alternative materials have been trialed including allograft or xenograft material, and polypropylene monofilament large pore mesh is commonly accepted around the world as the best material available for urethral slings.[43] The fact that the

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prolapse of the apical segment of the vagina: a systematic review and meta-analysis. Int Urogynecol J. 2016 Mar 7;27(3):355-366.

[38] Siddiqui NY, et al., Mesh Sacrocolpopexy Compared With Native Tissue Vaginal Repair: A Systematic Review and Meta-analysis. Obstet Gynecol. 2015 Jan;125(1):44-55.

[39] Costantini E, et al., Sacrocolpopexy for pelvic organ prolapse: evidence-based review and recommendations. Eur J Obstet Gynecol Reprod Biol. 2016 Oct;205:60-5. doi: 10.1016/j.ejogrb.2016.07.503. Epub 2016 Aug 3.

[40] Gilleran JP, et al., Robotic-assisted laparoscopic mesh sacrocolpopexy. Ther Adv Urol. 2010 Oct-Dec;2(5-6):195-208.

[41] Ford AA, et al., Mid-urethral sling operations for stress urinary incontinence in women. Cochrane Database Syst Rev. 2015 Jul 1;(7):CD006375.

[42] Baylón K, et al., Past, Present and Future of Surgical Meshes: A Review. Membranes (Basel). 2017 Aug 22;7(3).pii:E47; Lockhart K, et al., Mesh versus non-mesh for inguinal and femoral hernia repair. Cochrane Database Syst Rev 2018 Sep 13;9:CD011517.

[43] Nager C, et al., Position statement on mesh midurethral slings for stress urinary incontinence. Female Pelvic Med Reconstr Surg. 2014 May-Jun;20(3):123-5; ; Schimpf MO, et al, Sling surgery for stress urinary incontinence in women: a systematic review and metaanalysis. Am J Obstet Gynecol. 2014 Jul;211(1):71.e1-71.e27; Ford AA, et al., Mid-urethral sling operations for stress urinary incontinence in women. Cochrane Database Syst Rev. 2017 Jul 31;7:CD006375.

Prolene mesh and Gynemesh PS are macroporous allows for excellent tissue ingrowth, and results in a low infection rates. The fact that the meshes have been well-studied gives me confidence as a surgeon that I know the potential risks and benefits of the devices and can counsel my patients effectively regarding their treatment options. The fact that the meshes come sterilized is a positive design attribute, as that also reduces the potential for infection. The utilization of Prolene polypropylene mesh in the devices is desirable because the graft is of a consistent durability, strength, availability, and quality, thereby avoiding the possibility of suboptimal quality of the native tissue used with native tissue repairs.

Barber and colleagues noted in 2013 that abdominal sacrocolpopexy utilizing polypropylene mesh yields superior outcomes compared to procedures utilizing biological materials such as fascia lata, porcine dermis, and small intestine submucosa.[44] The Prolene mesh is lightweight, Type 1 polypropylene mesh that has been extensively studied in various pelvic floor surgeries. There are lighter-weight, larger-pore meshes available, but published literature does not show that their use causes significantly reduced complications. Published literature regarding lighter-weight and larger pore meshes used in pelvic floor surgeries shows that the use of those meshes does not avoid the risks involved with the use of mesh like the Gynecare Prolene mesh or Gynemesh PS; dyspareunia and mesh exposure can still occur.[45]

Prolene mesh and Gynemesh PS are safe and effective for use in sacrocolpopexy, and the benefits of using the mesh outweigh the risks of using the meshes in appropriately selected patients.

V. Response to Contentions by Plaintiffs' Experts

The mesh used in the Prolene mesh and Gynemesh PS is made of Prolene polypropylene, which has been used in surgeries for decades. This mesh is a large pore Type I macroporous, lightweight mesh, which is known for its biocompatibility.[46] Prolene mesh has a pore size in excess of 1 mm, and Gynemesh PS has a 2.5 mm pore size. The pore size of both meshes' is much larger than the 75 µm required to be considered Type I mesh. The Gynemesh PS incorporates blue lines (also made of Prolene polypropylene suture) that assist the surgeon with placement of the mesh. The Prolene mesh weighs 90-95 g/m^2, whereas the Gynemesh PS that became available in 2002 weighs 43 g/m^2, which was requested by surgeons who were seeking lighter weight sacrocolpopexy meshes. Polypropylene suture has been used for decades in cardiac, general, gynecologic, orthopedic, thoracic, and urologic surgery. Polypropylene mesh was first used in surgery to repair abdominal wall hernia in 1958 and has been used extensively in humans for this purpose for the past 30 years.[48] A variety of materials have been tried over

[44] Barber MD and Maher C, Apical prolapse. Int Urogynecol J. 2013;24:1815-33.
[45] Milani AL, et al., Trocar-guided mesh repair of vaginal prolapse using partially absorbable mesh: 1 year outcomes. Am J Obstet Gynecol 2011;204:74.e1-8.
[46] Ford AA, et al., Mid-urethral sling operations for stress urinary incontinence in women. Cochrane Database Syst Rev. 2015 Jul 1;(7):CD006375.
[48] Baylón K, et al., Past, Present and Future of Surgical Meshes: A Review. Membranes (Basel). 2017 Aug 22;7(3); Lockhart K, et al., Mesh versus non-mesh for inguinal and femoral hernia repair. Cochrane Database Syst Rev. 2018 Sep 13;9:CD011517.

time and polypropylene monofilament large pore mesh is commonly accepted around the world as the best material available for midurethral slings and sacrocolpopexy.[49]

Some plaintiffs' experts contend that the Prolene polypropylene mesh degrades in vivo, resulting in pain and other complications. I have not seen evidence of this in my practice, and the level 1 clinical evidence pertaining to polypropylene sacrocolpopexy mesh does not support this theory. The theory that Prolene polypropylene degrades in vivo is belied by the extensive body of data supporting the efficacy and safety of the devices made of the Prolene polypropylene mesh used in the sacrocolpopexy mesh. A recent article by Thames and colleagues found that the cracked layer on the outside of an explanted polypropylene fiber identified as degraded Prolene by some researchers is actually "an adsorbed protein-formaldehyde coating, resulting from the well-established formalin-protein fixation process, which occurs immediately upon placing an explant in formalin."[50] Similarly, de Tayrac and Letouzey found that the surface cracking on explanted polypropylene mesh was a biofilm that, once removed, revealed no degradation of the polymer.[51] The Clavé article frequently relied on by plaintiffs' experts as evidence of polypropylene degradation notes that the authors could not confirm their hypotheses regarding polypropylene degradation, including whether or not direct oxidation of the polypropylene occurred in vivo. The authors also only analyzed 1/3 of the explanted specimens that were available to be analyzed.[52]

Some plaintiffs' experts contend that the Prolene mesh or the Gynemesh PS is too heavy. However, a recent study showed that patients receiving a sacrocolpopexy mesh that weighed less than 20 g/m^2 had double the risk of failure of the procedure in the anterior compartment within the first three years following surgery compared to patients who received a mesh that weighed less than 35 g/m^2.[53] Biologic or other graft materials have not been demonstrated to be more effective or safer than macroporous polypropylene meshes like Prolene mesh and Gynemesh PS.[54]

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[49] Ford AA, et al., Mid-urethral sling operations for stress urinary incontinence in women. Cochrane Database Syst Rev. 2017;7:CD006375; Schimpf MO, et al., Sling surgery for stress urinary incontinence in women: a systematic review and metaanalysis. Am J Obstet Gynecol 2014;211(1):71.e1-71.e27; AUGS & SUFU Position Statement on Mesh Midurethral Slings for Stress Urinary Incontinence (Jan. 2014); Cundiff GW, et al., Pelvic Floor Disorders Network. Risk factors for mesh/suture erosion following sacral colpopexy. Am J Obstet Gynecol. 2008 Dec;199(6):688.e1-5.

[50] Thames SF, et al., The myth: in vivo degradation of polypropylene-based meshes. Int Urogynecol J. 2017 Feb;28(2):285-97.

[51] De Tayrac R and Letouzey V, Basic science and clinical aspects of mesh infection in pelvic floor reconstructive surgery. Int Urogynecol J. 2011 Jul;22(7):775-80.

[52] Clavé A, et al.., Polypropylene as a reinforcement in pelvic surgery is not inert: comparative analysis of 100 explants. Int Urogynecol J. 2010;21:261-70.

[53] Askew AL, et al., Does Mesh Weight Affect Time to Failure After Robotic-Assisted Laparoscopic Sacrocolpopexy? Female Pelvic Med Reconstr Surg. 2018 Oct 12.

[54] Cundiff GW, et al., Pelvic Floor Disorders Network. Risk factors for mesh/suture erosion following sacral colpopexy. Am J Obstet Gynecol. 2008 Dec;199(6):688.e1-5; Kammerer-Doak DN, et al., Vaginal erosion of cadaveric fascia lata following abdominal sacrocolpopexy and suburethral sling urethropexy. Int Urogynecol J Pelvic Floor Dysfunct. 2002;13(2):106-109; Quiroz LH, et al., Abdominal sacrocolpopexy: anatomic outcomes and complications with Pelvicol, autologous and synthetic graft materials. Am J Obstet Gynecol. 2008 May;198(5):557.e1-5; Gilleran JP, et al., Robotic-assisted laparoscopic mesh sacrocolpopexy. Ther Adv Urol. 2010 Oct;2(5-06):195-208.

Likewise, the extensive data supporting the safety and efficacy of sacrocolpopexy mesh does not support the theory that the Prolene polypropylene is cytotoxic or elicits an intense chronic foreign body reaction. Falconer and colleagues demonstrated that the inflammatory response to implantation of Prolene polypropylene was minimal.[55] That is consistent with my own experience using Prolene mesh and Gynemesh PS in sacrocolpopexies, and with the body of literature discussed in this report including systematic reviews, randomized controlled trials, long-term studies, and registry studies demonstrating low rates of complications—including but not limited to pain—with the use of the devices. Ethicon studied whether the Prolene polypropylene mesh in the TVT device was cytotoxic, and while it found "some evidence to suggest that the [polypropylene] mesh from the [TVT] may have cytotoxic potential," it concluded that "the cytotoxicity of the [polypropylene] mesh observed in vitro does not translate into any clinical significance or adverse patient outcomes" when factoring in relevant clinical evidence.[56]

Native tissue repairs use suture material and thus do not implant any graft material. Native tissue repairs such as uterosacral ligament suspensions and sacrospinous ligament fixations carry inherent risks such as failure, suture exposure (if permanent suture is used), and granulation tissue. The OPTIMAL trial 5-year data shows that uterosacral ligament suspensions had a 61% failure rate at 5-year follow-up and sacrospinous ligament fixations had a 70% failure rate. The procedures had 5-year suture exposure rate of 26%.[57] They also carry a risk of post-operative pain, as does any prolapse procedure.[58] The sub-optimal outcomes achieved with native tissue repairs are what led surgeons to begin using graft materials in prolapse repairs.

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[55] Falconer C, et al., Influence of Different Sling Materials on Connective Tissue Metabolism in Stress Urinary Incontinent Women. Int Urogynecol J. 2001 (Suppl 2):S19-S23.

[56] T. Barbolt Memo re Cytotoxicity Risk Assessment for the TVT (Ulmsten) Device, Aug. 8, 1997, at 1. ETH.MESH.00349228.

[57] Jelovsek JE, et al., Effect of Uterosacral Ligament Suspension vs Sacrospinous Ligament Fixation With or Without Perioperative Behavioral Therapy for Pelvic Organ Vaginal Prolapse on Surgical Outcomes and Prolapse Symptoms at 5 Years in the OPTIMAL Randomized Clinical Trial. JAMA. 2018;319(15):1554-65; Toglia MR, and Fagan MJ, Suture erosion rates and long-term surgical outcomes in patients undergoing sacrospinous ligament suspension with braided polyester suture. Am J Obstet Gynecol 2008;198:600.e1-600.e4; Yazdany T, et al., Suture complications in a teaching institution among patients undergoing uterosacral ligament suspension with permanent braided suture. Int Urogynecol J. 2010 Jul;21(7):813-818.

[58] Unger CA, et al., Incidence of adverse events after uterosacrocolpopexy for uterovaginal and posthysterectomy vault prolapse. Am J Obstet Gynecol 2015;212:603.e1-7; Wieslander CK, et al., Uterosacral ligament suspension sutures: Anatomic relationships in unembalmed female cadavers. Am J Obstet Gynecol 2007;197:672.e1– 6; Lowenstein L, et al., Neural pain after uterosacral ligament vaginal suspension. Int Urogynecol J Pelvic Floor Dysfunct. 2007 Jan;18(1):109-10; Siddique SA, et al., Relationship of the uterosacral ligament to the sacral plexus and to the pudendal nerve. Int Urogynecol J Pelvic Floor Dysfunct 2006;17:642-645; Collins SA, et al., Nerve injury during uterosacral ligament fixation: a cadaver study. Int Urogynecol J Pelvic Floor Dysfunct 2009 Jan 27; Barber MD, et al., Comparison of 2 transvaginal surgical approaches and perioperative behavioral therapy for apical vaginal prolapse: the OPTIMAL randomized trial. JAMA. 2014;311(10):1023-1034; Rardin CR, et al., Uterosacrocolpopexy at the time of vaginal hysterectomy, J Reprod Med. 2009 May; 54(g)273-280; Edenfield AL, et al., Vaginal prolapse recurrence after uterosacral ligament suspension in normal-weight compared with overweight and obese women. Obstet Gynecol. 2013 Mar;121(3):554-9.

Both my clinical experience using the sacrocolpopexy mesh and the published literature regarding such mesh demonstrates that the mesh does not contract or shrink to a clinically significant extent. Literature evaluating this issue in the context of Prolene polypropylene mesh midurethral slings supports this.[61]

The pore size of the sacrocolpopexy mesh is macroporous and allows for tissue ingrowth, while still allowing for macrophages and leukocytes to transverse the pores, reducing the risk of infection.[62]

There is considerable evidence that polypropylene does not cause cancer. In a large population-based study from Sweden of more than 5 million women, including all (almost 21,000) women that had undergone MUS surgery since 1997, they found that the type 1 polypropylene mesh used in midurethral slings is not associated with increased cancer risk.[63] This is the same mesh type that is used in the sacrocolpopexy mesh.

VI. IFU and Other Educational Materials

In my opinion, the Prolene polypropylene mesh IFU and Gynemesh PS IFU provided appropriate information for surgeons to be able to use the meshes safely. They included information regarding the potential risks associated with the meshes and specific properties of the mesh. The indications for use of the Gynemesh PS are included in the Gynemesh PS IFU—noting it is indicated for use in treating pelvic organ prolapse.[64] The Prolene mesh IFU indicates that the mesh is for use in reinforcing hernias and other fascial defects that need the addition of a reinforcing or bridging material. devices, contraindications, and instructions on how to implant the devices. They also contained warnings and potential adverse reactions. The "Performance" or "Actions" section of the IFUs notes that Prolene mesh elicits a minimal inflammatory reaction in tissue based on animal studies, and that the reaction is transient and followed by the deposition of a thin fibrous layer of tissue which can grow through the interstices of the mesh, incorporating it into adjacent tissue. Based on my experience implanting a large number of Prolene and Gynemesh PS polypropylene meshes, these are accurate statements.

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[61] Nilsson CG, et al., Seventeen years' follow-up of the tension-free vaginal tape procedure for female stress urinary incontinence. Int Urogynecol J 2013 Aug;24(8):1265–1269; Lo T-S, et al., Ultrasound Assessment of Mid-Urethra Tape at Three-Year Follow-Up After Tension-Free Vaginal Tape Procedure. J Urol 2004;63(4):671-5; Dietz HP, et al., Does the tension-free vaginal tape stay where you put it? Am J Obstet Gynecol 2003;188:950-3; Lukacz ES, et al., The effects of the tension-free vaginal tape on proximal urethral position: a prospective longitudinal evaluation. Int Urogynecol J. 2003;14:179-84.

[62] Amid PK, Classification of biomaterials and their related complications in abdominal wall hernia surgery. Hernia 1997;1:15-21.

[63] Altman D, et al., Cancer Risk After Midurethral Sling Surgery Using Polypropylene Mesh. Obstet Gynecol 2018;131(3):469-74; King AB, et al., Is there an association between polypropylene midurethral slings and malignancy? Urology. 2014 Oct;84(4):789-92; Linder BJ, et al., Evaluation of the local carcinogenic potential of mesh used in the treatment of female stress urinary incontinence. Int Urogynecol J. 2016 Sep;27(9):1333-6.

[64] Gynemesh PS IFU. ETH.MESH.02342194-96 and ETH.MESH.08221377-80; Prolene Mesh IFU. ETH.MESH.02342102.

The IFU is used by surgeons who have been through—at a minimum—medical school and residency training and bring with them fundamental knowledge of surgical risks associated with any pelvic floor surgery such as a risk that the procedure will fail to cure the condition it was meant to treat, as well as temporary or chronic pain including dyspareunia. Residents are expected to gain an understanding of the indications for use of graft materials in pelvic reconstructive surgery, their characteristics, and potential complications associated with use of the grafts. They are also expected to understand the benefits and risks of the various prolapse repair procedures.[65] Fellows seeking advanced training in urogynecology should learn how to perform a variety of evidence-based surgical procedures for prolapse and to describe the indications, intra- and post-operative complications and success of a variety of prolapse surgeries, including both mesh and non-mesh surgeries.[66] In my opinion, the IFUs do not need to contain information regarding risks that are not evidence-based, clinically significant or information on risks that are commonly known by gynecologists, urologists, or urogynecologists.[67]

I think that physicians should read through IFUs for products they use but an IFU will never adequately provide all possible information. A recent survey of North American Urologists found that a minority (23.1%) of the survey respondents—79.3% of whom identified as general urologists and 12.7% as FPMRS-trained urologists—who reported placing a mesh prolapse repair kit had read the Instructions for Use.[68]

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[65] AUGS, Resident Learning Objectives.
[66] The American Board of Obstetrics and Gynecology and The American Board of Urology, Guide to Learning in Female Pelvic Medicine and Reconstructive Surgery 2012.
[67] 21 C.F.R. Pt. 801, Sec. 801.109(c).
[68] Kirkpatrick G, et al., Transvaginal Mesh Placement and the Instructions for Use: A Survey of North American Urologists. Urol Prac. 2019 Mar;6:135-39.